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Emergence of a Single Solid Chiral State from a Nearly Racemic Amino Acid Derivative

Wim L. Noorduyn,[†] Toshiko Izumi,[‡] Alessia Millemaggi,[§] Michel Leeman,^{||} Hugo Meekes,[†]
Willem J. P. Van Enkevort,[†] Richard M. Kellogg,^{*,||} Bernard Kaptein,^{*,§} Elias Vlieg,^{*,†} and
Donna G. Blackmond^{*,‡}

*IMM Solid State Chemistry, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, Netherlands,
Department of Chemistry and Department of Chemical Engineering, Imperial College, London SW7 2AZ U.K., DSM
Pharmaceutical Products—Advanced Synthesis, Catalysis & Development, P.O. Box 18,
6160 MD Geleen, Netherlands, and Syncom B.V., Kadijk 3, 9747 AT Groningen, Netherlands*

Received November 27, 2007; E-mail: r.m.kellogg@syncom.nl; Bernard.Kaptein@dsm.com; e.vlieg@science.ru.nl;

d.blackmond@imperial.ac.uk

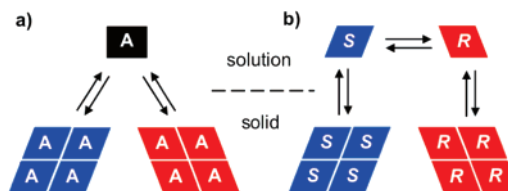
Understanding how the single-handedness of biological molecules came about has been of intense interest since Pasteur first separated mirror-image crystals of a tartrate salt.¹ Several models have been proposed to address the question of how enantiomerically pure solutions or crystalline phases could have emerged from a presumably racemic prebiotic world.^{2–9} Viedma⁶ recently demonstrated the inexorable and random emergence of solid-phase single chirality for the intrinsically achiral inorganic compound NaClO₃ initially present as a racemic mixture of two enantiomorphic solid phases in equilibrium with the achiral aqueous phase (Scheme 1a). Grinding the slurry of crystals with glass beads promotes dynamic dissolution/crystallization processes that result in the conversion of one solid enantiomorph into the other. The conversion relies on the fact that the solid-phase chiral identity of the intrinsically achiral NaClO₃ is lost upon dissolution.

An intriguing analogy to this simple demonstration of “chiral amnesia”¹⁰ is presented by a molecular system of true enantiomers that forms separate *R* and *S* solid-phase crystals (known as a conglomerate¹¹), and that can be induced to undergo racemization in solution.^{10,12} (Scheme 1b). We report here the first experimental proof-of-concept for the emergence of a single solid-phase chiral state for an intrinsically chiral molecule starting from a nearly racemic mixture of enantiomorphic crystals. This finding extends Viedma’s model to biologically relevant enantiomeric molecules, holding profound implications for our understanding of the origin of single chirality in living systems.

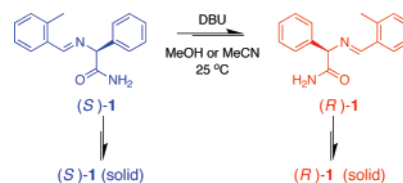
The imine of 2-methyl-benzaldehyde and phenylglycinamide **1** (Scheme 2) forms a conglomerate in the solid phase and racemizes rapidly in solution with added base (*t*_{1/2} < 2 min at 25 °C with the organic base DBU in MeOH, p*K*_a = 12). Solution-solid mixtures of **1** (4 g) at varying overall ee were magnetically stirred (1250 rpm) at ambient temperature in MeOH or MeCN (36 g) in the absence and in the presence of 2.5 mm glass beads (10 g). After establishing solution-solid equilibrium, solution-phase racemization was initiated by adding DBU (5 mol %). Samples of the solid were collected over time and the enantiomeric purity was measured using two independent chiral HPLC methods. Experiments were carried out in all participating laboratories.

In the presence of glass beads, which impart mechanical energy to the system inducing continuous attrition of the crystals, we found that the ee of the solid rises inexorably over time, evolving to a

Scheme 1. Analogy between Solid-Solution Equilibrium for (a) an Intrinsically Achiral Molecule; and (b) a Chiral Molecule Undergoing Solution-Phase Racemization



Scheme 2. Chemical and Physical Equilibria in the Racemization and Crystallization/ Dissolution Processes for **1**



single solid chiral state from an initial small imbalance in crystal composition as low as 2–3% ee (see Figure 1 (left) and Supporting Information). The solid of single chirality thus obtained is stable over time in the presence of the racemizing solution. For a stirred slurry in the absence of glass beads, the solid phase ee remained unchanged from its initial value.

This result demonstrates that a slight enantiom imbalance in **1** directs the trend to a single solid chiral state. We also observed that seeding a racemic system of crystals of **1** with chiral additives could also direct the establishment of a single chiral solid. For example, concentrations as low as 0.1 mol % enantiopure phenylglycine (Phg) as an additive provide a sufficient chiral bias for achieving attrition-induced solid-phase single chirality (Figure 1, right).^{13–16} (*S*)-Phg leads to an *R* chiral end state, (*R*)-Phg to *S* chirality, and with a resolution time that decreases for higher Phg concentrations.

These findings may be rationalized taking into account Viedma’s⁶ model involving a dynamic process of crystal dissolution and growth enhanced by attrition, along with considerations of total surface area as a driving force for crystal growth. According to the Gibbs–Thomson rule, smaller crystals produced by attrition dissolve more readily than larger ones. In a saturated solution, this leads to Ostwald ripening¹⁷ in which large crystals grow at the cost of smaller ones regardless of their handedness. A small imbalance in the handedness of large compared to small crystals may occur because of a small initial enantiomeric excess or may be induced by minute amounts of chiral species present in the solution. In the

[†] Radboud University Nijmegen.

[‡] Imperial College.

[§] DSM Pharmaceutical Products—Advanced Synthesis, Catalysis & Development.

^{||} Syncom B.V.

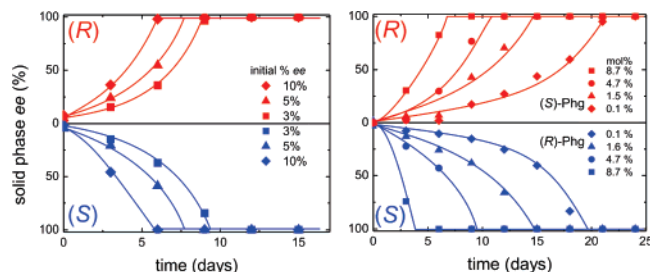


Figure 1. Attrition-enhanced evolution of solid-phase ee for **1** in MeCN: (left) starting from initial ee values of **1** as shown; (right) starting from racemic **1** with added Phg as shown. Lines are a guide to the eye.

latter case, Lahav's "rule of reversal"^{18,19} applies. The continued fragmentation of crystals by attrition also provides a relative increase in the surface area of the hand that has established an excess. Although crystal growth and dissolution have approximately equal rates under near equilibrium conditions, the attrition-enhanced asymmetry described here coupled with solution-phase racemization produces a net flow of mass allowing depopulation of one chiral solid state toward the other via the solution phase. Paradoxically, the "chiral amnesia" induced by solution racemization provides the driving force for the evolution of solid-phase single chirality.^{6,10}

Crystallization-induced transformations of conglomerates as a route to chiral purification is practiced extensively for diastereomers that epimerize in solution,²⁰ taking advantage of a difference in solubility. Our results stand in striking contrast to Dimroth's principle, which although applied today primarily to the separation of diastereomers, was originally formulated for the general case of coupled physical and chemical equilibria. According to this principle, a general system as shown in Scheme 1b of two solid enantiomorphs in equilibrium with a solution in which racemization occurs represents a balance such that solid-phase enrichment should not occur.^{20–22} In our example, the continuous grinding of the solid enantiomorphs creates the essential solubility gradient for the dissolution and recrystallization processes that drive the system until all the solid material of one enantiomer is converted to the solid of the opposite hand. Once a state of single chirality is achieved, the system is "locked", because primary nucleation to form and sustain new crystals from the opposite enantiomer in the racemizing solution is kinetically prohibited under the conditions of the experiment. This provides a stable, irreversible route to extremely enantiopure compounds in high yield and with productivity limited only by the amount of solid material present at the outset. These concepts may readily be extended to other chiral systems.

Thus the emergence of a state of solid-phase single chirality for true enantiomers may be achieved in a near equilibrium process through an interplay between attrition-catalyzed dissolution and Ostwald ripening of crystals. This route to single chirality may be compared with physical models invoking, on the one hand, thermodynamic control for solution-phase enantioenrichment,^{7,23} and on the other hand, "far-from-equilibrium" crystallization processes.^{2a,5,24,25}

The state of solid-phase single chirality for an enantiomeric compound that forms a conglomerate is not more stable than the racemic state for the same size and number of crystals¹² but simply represents a kinetic trap accessible on our time scale due to acceleration of both crystal dissolution/growth and racemization. Thermodynamics dictates that single chirality may ultimately be achieved over eons of time, as in a prebiotic scenario, even in the

absence of accelerating influences. Our results demonstrate for the first time that the concept of attrition-enhanced solid-phase enantioenrichment may be extended from simple achiral salts to include biologically relevant enantiomeric molecules such as those responsible for recognition, replication, and ultimately for the chemical basis of life.²⁶

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Supporting Information Available: Details concerning experimental and analytical procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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